have been developed.[163,][164]

Maternal antitoxin levels do affect the immune response of infants. Diphtheria antitoxin levels greater than 0.1 IU/mL inhibit the response to active immunization; no effect is seen at levels of less than 0.02 IU/mL.[165,][166] This is more likely to be of significance in areas where *C. diphtheriae* continues to circulate, resulting in high levels of antibody in mothers and their infants. However, it appears that high maternal antibody titers suppress, but do not prevent, adequate responses of infants to two doses of vaccine, and after the third dose the suppressive effect is gone.[167,][168] The half-life of diphtheria antitoxin has been estimated to be 30 days.[169]

After three doses of diphtheria toxoid, virtually all infants develop diphtheria titers greater than 0.01 IU/mL.[170] Geometric mean titers vary among vaccine preparations, with some DTaP products producing significantly lower geometric mean titers than those observed after vaccination with DTP;[155] however, these differences are unlikely to be clinically significant. When the toxoid is used for primary immunization of adults, data suggest that virtually all adults develop diphtheria antitoxin titers greater than 0.01 IU/mL after administration of three doses of diphtheria toxoid, and that most develop titers greater than 0.1 IU/mL.[171]

Vaccination with protein conjugate vaccines containing diphtheria toxoid may result in a booster response to the carrier protein in persons who have previously received diphtheria toxoid.[172] One of the tetravalent meningococcal polysaccharide diphtheria toxoid conjugate vaccines currently licensed in the United States (Menactra, Sanofi Pasteur) contains approximately six times as much diphtheria toxoid as is contained in the adult formulations of Td vaccine. Simultaneous administration of Td and Menactra resulted in much higher geometric mean titers of diphtheria antitoxin than did Td (120.0 IU/mL compared with 8.4 IU/mL); consistent with the increase in diphtheria toxoid content, Menactra alone was also substantially more immunogenic than Td alone (46.5 IU/mL).[173] There is also cross-reactivity between diphtheria toxoid and CRM_{197} in protein conjugate vaccines; the other tetravalent meningococcal polysaccharide conjugate vaccine licensed in the United States (Menveo, Novartis Vaccines and Diagnostics) uses CRM_{197} as the protein carrier. Children receiving meningococcal serogroup C–CRM_{197} vaccines develop higher diphtheria antitoxin levels than are seen in children who did not receive the vaccine.[174,][175] Lack of baseline immunity to diphtheria may result in poor antibody responses to vaccines conjugated to CRM_{197}.[176] Although immunologic interference is a potential concern with simultaneous administration of diphtheria toxoid with diphtheria toxoid or CRM_{197}-containing protein conjugate vaccines,[177–179] experience to date does not suggest that the immunogenicity of diphtheria toxoid is adversely affected by simultaneous administration with these vaccines.

Correlates of protection

Several lines of evidence suggest that persons with diphtheria antitoxin levels of less than 0.01 IU/mL should be considered susceptible. Ipsen reported results of studies in which rabbits were administered antitoxin and then challenged with intravenously administered diphtheria toxin; rabbits with a serum level of 0.01 IU/mL were almost completely protected from death with the standard lethal dose.[180] However, higher doses of toxin required higher serum antitoxin levels for equivalent protection. On the basis of studies of diphtheria antitoxin levels early in the course of disease, persons with diphtheria antitoxin levels of less than 0.01 IU/mL appear to be highly susceptible to disease, and higher levels are generally associated with progressively less severe symptoms.[180–183] Probably no level of circulating antitoxin confers absolute protection; Ipsen reported two cases of fatal diphtheria in patients with antitoxin levels above 30 IU/mL the day after onset of symptoms.[180] Historically, clinical diphtheria was rare among persons with a negative Schick test; the minimal serum antitoxin level associated with a negative Schick test was approximately 0.005 IU/mL.[184] Overall, the data allow some general conclusions regarding protective levels in most circumstances. An antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection, and 0.1 IU/mL is considered a protective level of circulating antitoxin. Levels of 1.0 IU/mL and greater are associated with long-term protection.[185]

Efficacy and effectiveness of vaccine

No controlled clinical trial of the efficacy of the toxoid in preventing diphtheria has ever been conducted. There is, however, strong evidence from observational studies to support the effectiveness of vaccination. Some evidence of the protective efficacy of diphtheria toxoid is provided by observations during the Halifax epidemic.[114] During the course of this outbreak, an intense effort was made to administer diphtheria toxoid to previously unimmunized individuals, and the subsequent incidence of diphtheria in these children was compared with the incidence in the unimmunized population during the next few months. Among those immunized, the monthly incidence of diphtheria fell to 24.5 per 100,000 population, about one seventh of the rate in the unimmunized children during that same period (168.9 per 100,000). In Britain in 1943, the rate of clinical diphtheria among the unimmunized was 3.5 times that among the immunized, and mortality was 25-fold greater.[113] In an outbreak in Elgin, Texas, in 1970, only two of 205 fully immunized, exposed elementary

schoolchildren acquired the disease.[186] In contrast, among 97 children who had received inadequate or no immunization, a 13% attack rate occurred.

In a household study during a diphtheria outbreak in San Antonio, Texas, in 1970, vaccine efficacy was estimated at only 54%.[187] However, because index cases were included and denominators of exposed individuals were unknown, the data are difficult to interpret. Furthermore, any differences in attack rates between immunized and nonimmunized persons might have been blunted by the institution of antibiotic therapy in all members of the household on recognition of a case. Thus, the apparent efficacy of 54% is probably low. In an outbreak in Yemen, the protective efficacy of diphtheria toxoid was determined to be 87% by the case-control method.[103]

The effectiveness of Russian-manufactured diphtheria toxoid was evaluated in several case-control studies during the epidemic in the former Soviet Union. Three or more doses of diphtheria toxoid were demonstrated to be highly effective in prevention of diphtheria among children younger than 15 years in a preliminary study in Ukraine in 1992 and a subsequent study performed in Moscow in 1993. In Ukraine, the effectiveness of three or more doses was 98.2% (95% confidence interval [CI], 90.3%-99.9%).[188] In Moscow, the effectiveness of three or more doses was 96.9% (95% CI, 94.3%-98.4%), increasing to 99.0% for five or more doses (95% CI, 97.7%-99.6%).[189] In addition, administration of a booster dose of diphtheria toxoid within 2 years was shown to decrease risk of diphtheria among children 6 to 8 years of age compared with those who had received the last dose 3 to 4, or 5 to 7 years previously.[190] Among adults in the Russian Federation, the effectiveness of three or more doses compared with no doses was 70% (95% CI, 10%-90%).[191] Similarly, recent vaccination also was found to be highly effective among adults in Ukraine.[192]

Thus, it appears that the effectiveness of diphtheria toxoid is high but not 100%. However, most reports indicate that the disease in previously immunized individuals is milder and less likely to be fatal.[116,][117,][186,][193–195] In Britain in 1943, case-fatality rates in unimmunized children were more than sevenfold greater than rates in those who had been immunized (6.4% versus 0.9%).[113] The failure to protect 100% of individuals on exposure indicates the importance of herd immunity in the disappearance of diphtheria from developed countries.[196]

Duration of immunity and protection

Both the diphtheria toxoid formulation and the schedule of administration affect the level of diphtheria antitoxin achieved and the duration of protection. Globally, various schedules for primary immunization of infants are used, but after three doses of diphtheria toxoid, most children achieve antitoxin titers greater than the minimally protective level.[197] However, in the absence of ongoing exposure, immunity wanes over time, requiring booster doses of diphtheria toxoid to maintain protective antitoxin levels. Longitudinal studies indicate that after a period of rapid decline of antitoxin levels, there is a prolonged, slower decline, presumably reflecting the initially activated immune system and half-life of immunoglobulin, followed by a sustained period of less active production of immunoglobulin.[198,][199] Both the four-dose schedule used in the United States, with 15 Lf doses at 2, 4, 6, and 15 months of age, and the three-dose schedule used in Sweden, Denmark, and Norway, administering 25 Lf doses at 3, 5, and 12 months of age, resulted in geometric mean levels well in excess of the minimally protective level at 48 months of age.[200] Similar geometric mean levels were found 23 months after dose three administered as DT (pediatric diphtheria and tetanus toxoids), DTP, or DTaP, with varying diphtheria toxoid contents in a two, four, and six-dose schedule.[199] In 1990, the United Kingdom moved to an accelerated schedule, administering DTP at 2, 3, and 4 months instead of at 3, 5, and 9 months of age. Although postvaccination geometric mean concentrations of diphtheria antitoxin were lower among children vaccinated on the accelerated schedule, geometric mean antitoxin levels did not differ at age 4 years among children who completed the series at 8 to 13 months, 6 to 7 months, or before 6 months of age, suggesting that adequate protection would be maintained until administration of the preschool booster dose.[201–203]

Although various schedules for primary immunization appear to provide adequate protection from diphtheria in the early years of life, in the absence of a booster dose at 4 to 6 years, protection may not be maintained throughout the school-age years. In Sweden, the first booster dose after the primary series is not administered until age 10, resulting in lower levels of antitoxin among children 5 to 9 years of age than is observed in countries administering a preschool-age booster.[204] In one recent study, 12% of 10-year-old children had diphtheria antitoxin levels below 0.01 IU/mL before receipt of a booster dose.[205] In the Soviet Union, the immunization schedule was changed in 1986, delaying the age 6 (years) booster dose to age 9. During the diphtheria outbreak in Russia in the 1990s, receipt of the booster dose at 6 to 8 years of age was found to decrease the risk of diphtheria in this age group.[190] In countries with long-standing childhood immunization programs, adults who have neither been exposed to diphtheria nor received booster doses of diphtheria toxoid may become susceptible to diphtheria as a result of waning immunity.[197] During the outbreak in the former Soviet Union, waning of immunity was thought to contribute to the high incidence rate observed among adults. A